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**APPLICATION NUMBER: 60/528,892**

**FILING DATE: *December 11, 2003***

**RELATED PCT APPLICATION NUMBER: *PCT/US04/41374***



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## PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. EU 861356146 US

INVENTOR(S)					
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)			
Jack	Elias	Woodbridge, CT			
<input type="checkbox"/> Additional inventors are being named on the ___ separately numbered sheets attached hereto					
TITLE OF THE INVENTION (280 characters max)					
CCR5 blockage in emphysema					
Direct all correspondence to: <b>CORRESPONDENCE ADDRESS</b> <input type="checkbox"/> Customer Number <span style="border: 1px solid black; display: inline-block; width: 150px; height: 20px; vertical-align: middle;"></span> → <span style="border: 1px solid black; padding: 5px; display: inline-block; width: 150px; height: 30px; vertical-align: middle;">Place Customer Number Bar Code Label here</span> OR <input checked="" type="checkbox"/> Firm or Individual Name <span style="border: 1px solid black; display: inline-block; width: 300px; height: 20px; vertical-align: middle;">Yale University, Office of Cooperative Research</span> Address <span style="border: 1px solid black; display: inline-block; width: 300px; height: 20px; vertical-align: middle;">433 Temple Street</span> Address <span style="border: 1px solid black; display: inline-block; width: 300px; height: 20px; vertical-align: middle;"></span> City <span style="border: 1px solid black; display: inline-block; width: 100px; height: 20px; vertical-align: middle;">New Haven</span> State <span style="border: 1px solid black; display: inline-block; width: 50px; height: 20px; vertical-align: middle;">CT</span> ZIP <span style="border: 1px solid black; display: inline-block; width: 50px; height: 20px; vertical-align: middle;">06511</span> Country <span style="border: 1px solid black; display: inline-block; width: 100px; height: 20px; vertical-align: middle;">USA</span> Telephone <span style="border: 1px solid black; display: inline-block; width: 100px; height: 20px; vertical-align: middle;">(203) 436-8096</span> Fax <span style="border: 1px solid black; display: inline-block; width: 100px; height: 20px; vertical-align: middle;">(203) 436-8086</span>					
ENCLOSED APPLICATION PARTS (check all that apply)					
<input checked="" type="checkbox"/> Specification Number of Pages <span style="border: 1px solid black; display: inline-block; width: 50px; height: 20px; vertical-align: middle;">2</span>		<input type="checkbox"/> CD(s), Number <span style="border: 1px solid black; display: inline-block; width: 50px; height: 20px; vertical-align: middle;"></span>			
<input checked="" type="checkbox"/> Drawing(s) Number of Sheets <span style="border: 1px solid black; display: inline-block; width: 50px; height: 20px; vertical-align: middle;">26</span>		<input type="checkbox"/> Other (specify) <span style="border: 1px solid black; display: inline-block; width: 150px; height: 20px; vertical-align: middle;"></span>			
<input type="checkbox"/> Application Data Sheet. See 37 CFR 1.76					
METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT					
<input checked="" type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. <input type="checkbox"/> A check or money order is enclosed to cover the filing fees <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: <span style="border: 1px solid black; display: inline-block; width: 100px; height: 20px; vertical-align: middle;">25-0110</span> <input type="checkbox"/> Payment by credit card. Form PTO-2038 is attached.					<b>FILING FEE AMOUNT (\$)</b> <span style="border: 1px solid black; display: inline-block; width: 80px; height: 40px; vertical-align: middle; text-align: center; line-height: 40px;">\$80.00</span>
The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government. <input type="checkbox"/> No. <input checked="" type="checkbox"/> Yes, the name of the U.S. Government agency and the Government contract number are: <span style="border: 1px solid black; display: inline-block; width: 200px; height: 20px; vertical-align: middle;">NHLBI HL 66571</span>					

Respectfully submitted,

SIGNATURE

TYPED or PRINTED NAME Olga Rivera

TELEPHONE

(203) 785-2005

Date 12/11/03

REGISTRATION NO.  
(if appropriate)  
Docket Number:

1617

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This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the complete provisional application to the PTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C. 20231.

7548 U.S. PTO 60/528892

121103

**Subject:** CCR 5

**From:** Jack Elias <jack.elias@yale.edu>

**Date:** Wed, 10 Dec 2003 18:54:59 -0500

**To:** John Puziss <john.puziss@yale.edu>

**CC:** kathy bertier <kathleen.bertier@yale.edu>

John

Kathy from my office will be sending you a zip with a set of powerpoint slides demonstrating the effects of antibody and genetic neutralization/ablation of CCR 5 in the IL-13 and gamma interferon mice. (They are too big to send by E-mail). As you can see, both interventions decreased emphysema and inflammation (Th2-like in the case of IL-13 and Th1-like in the case of gamma). In the case of the IL-13 mice the elimination of CCR5 also increased survival. Other items to note are the ability of the CCR5 based interventions to

1. decrease TNF production
2. decrease IL-13 induced apoptosis (assessed by TUNEL staining)
3. decrease gamma interferon and IL-13-induced chemokine production including MCP-1, MIP-1alpha, MIP-1 beta, KC, IP-10

Thus we believe CCR 5 blockade can diminish IL-13 (Th2) and gamma interferon (Th1) induced inflammation, remodeling, emphysema and apoptosis

Call me if you have questions

Jack

# Methods

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**CC10-IL-13 transgenic mice**

**CC10-IL-4 transgenic mice**

**CC10-rtTA-IL-13 transgenic mice**

**CC10-rtTA-IFN- $\gamma$  transgenic mice**

**Anti - CCR5 monoclonal antibody**

**CCR5KO mice**

**From Jackson Lab**

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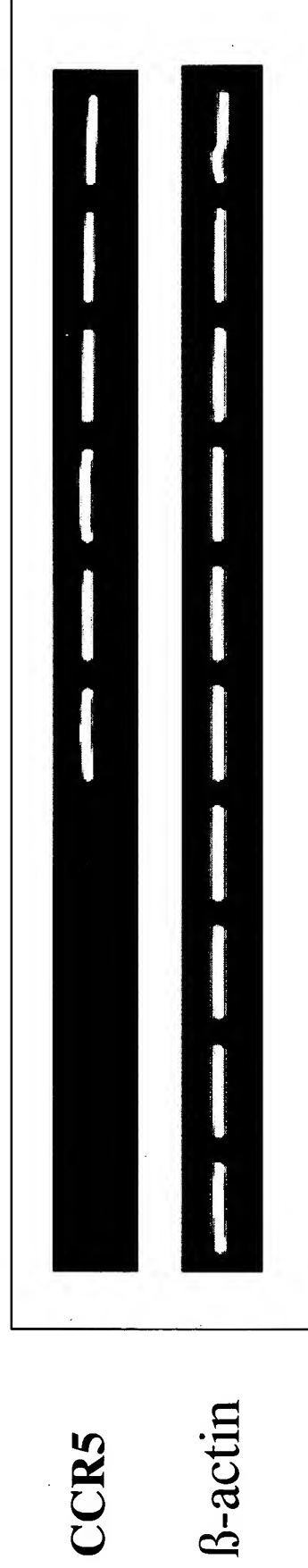
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**Stimulation of CCR5 gene expression by IL-13, IL-4 and  
gamma interferon in vivo**

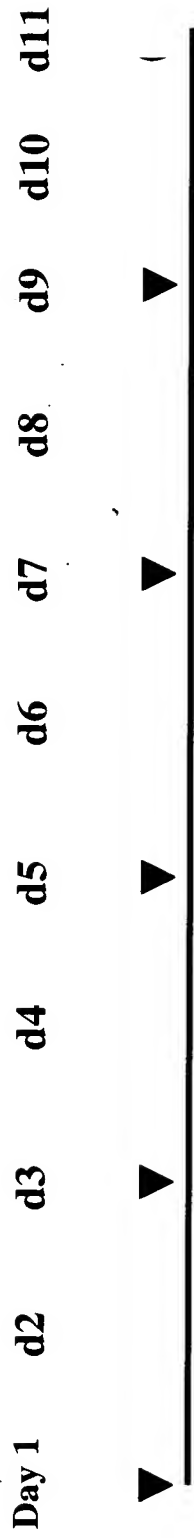
<b>IL-4</b>	-	+
<b>IL-13</b>	-	+
<b>IFN-<math>\gamma</math> (C57B/6)</b>	-	+
<b>IFN-<math>\gamma</math> (Balb/c)</b>	-	+



# Protocol for anti-CCR5 treatment

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Anti-CCR5 antibody given every other day by i.p.  
500µg per time.



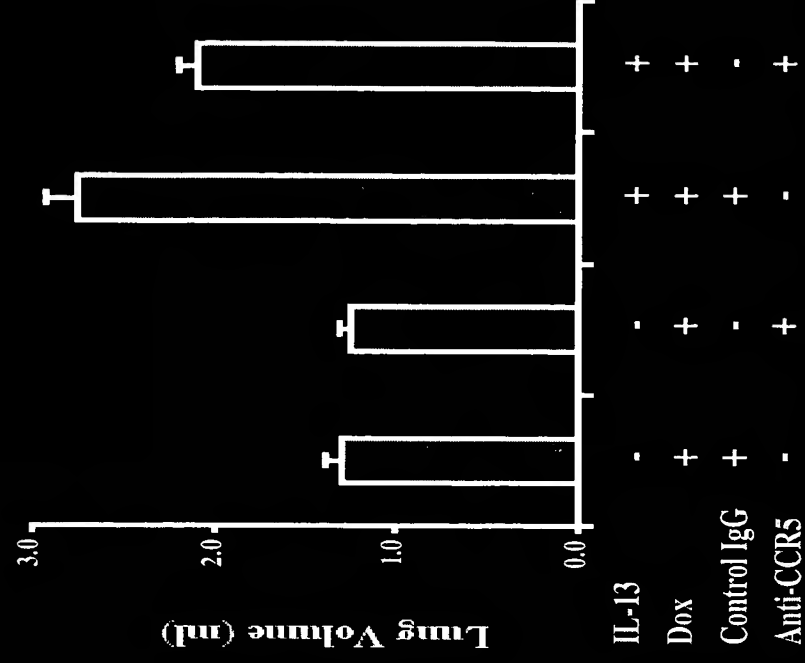
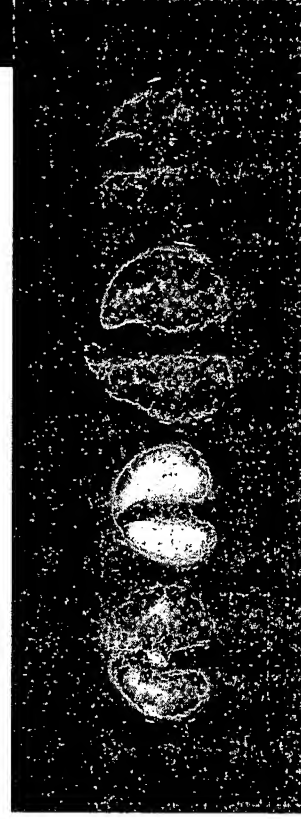
Dox on

Sacrifice

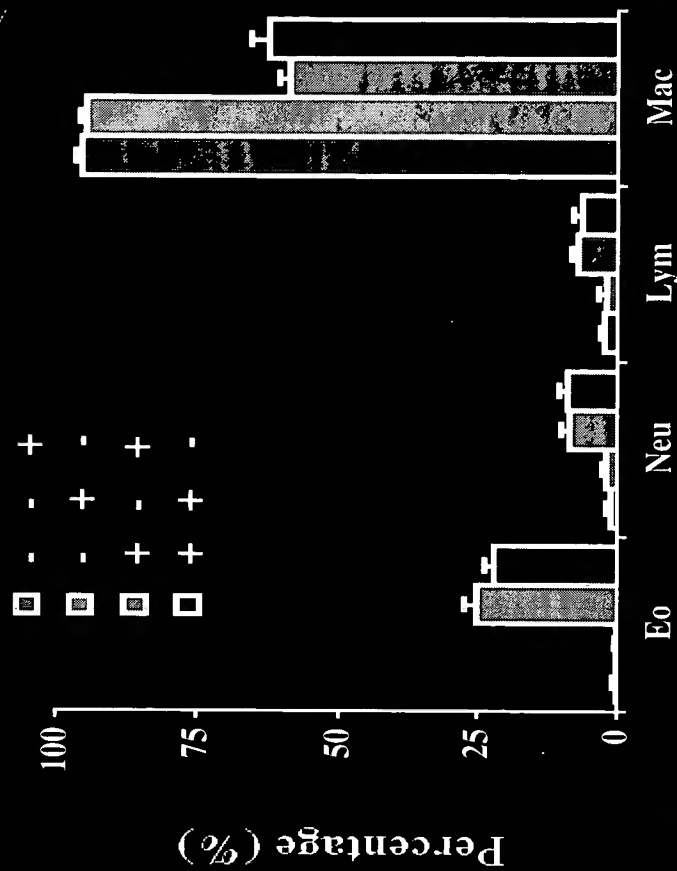
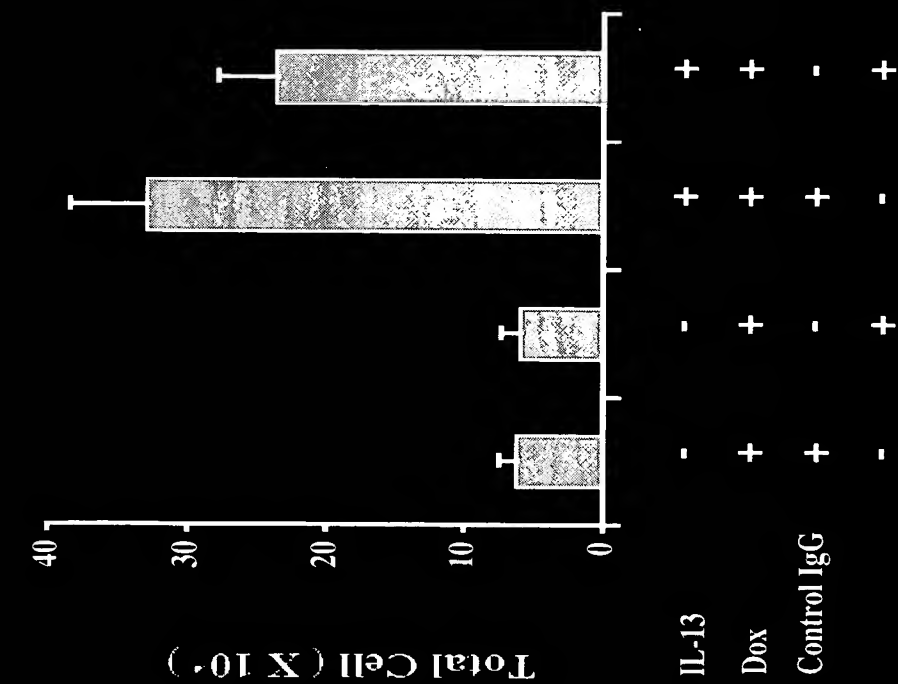


# Effect of anti-CCR5 on IL-13-induced increase in lung volume

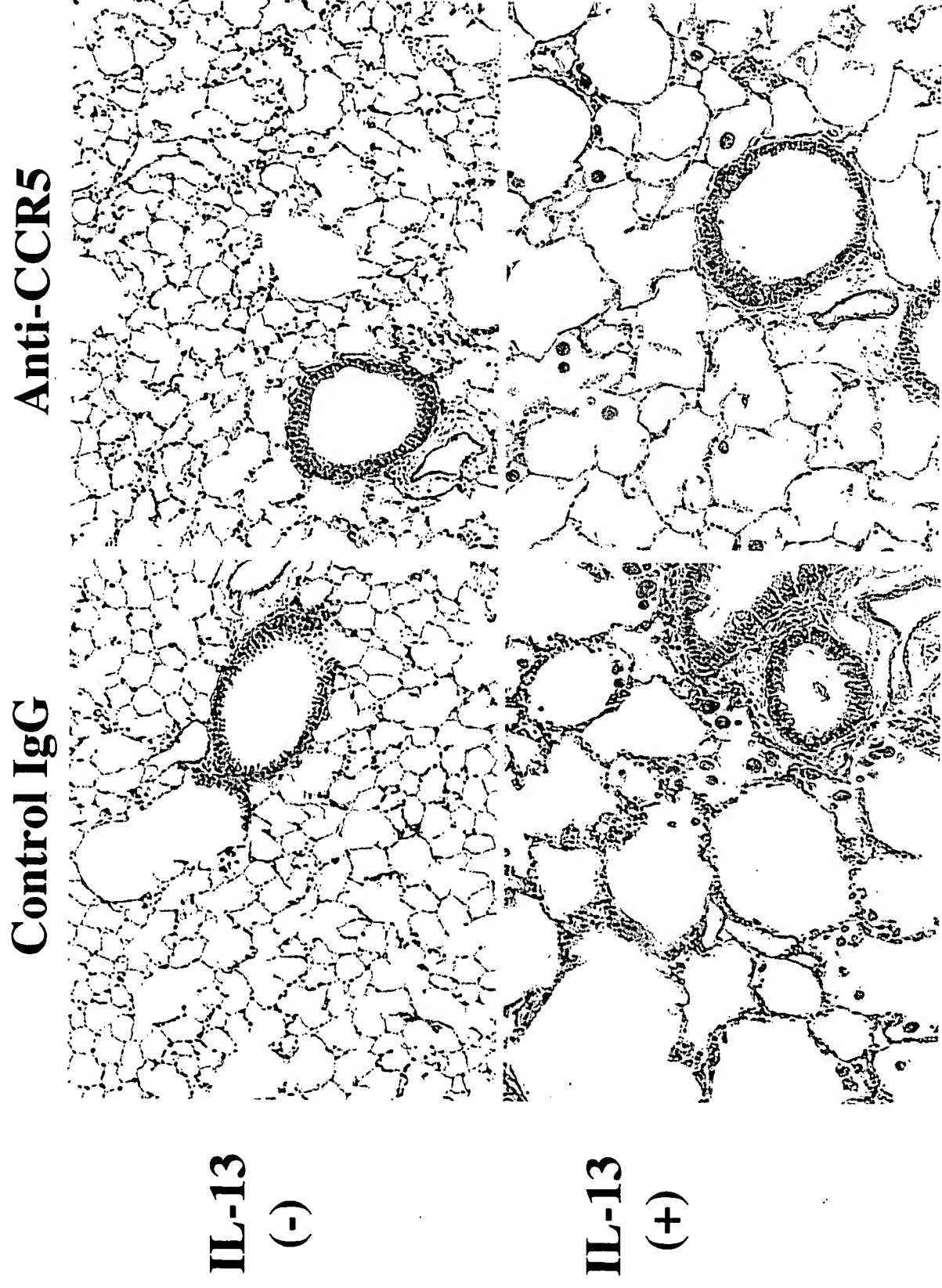
Control IgG	+	-	+	-
Anti-CCR5	-	+	-	+
Dox	+	+	+	+
iIL-13	-	-	-	+



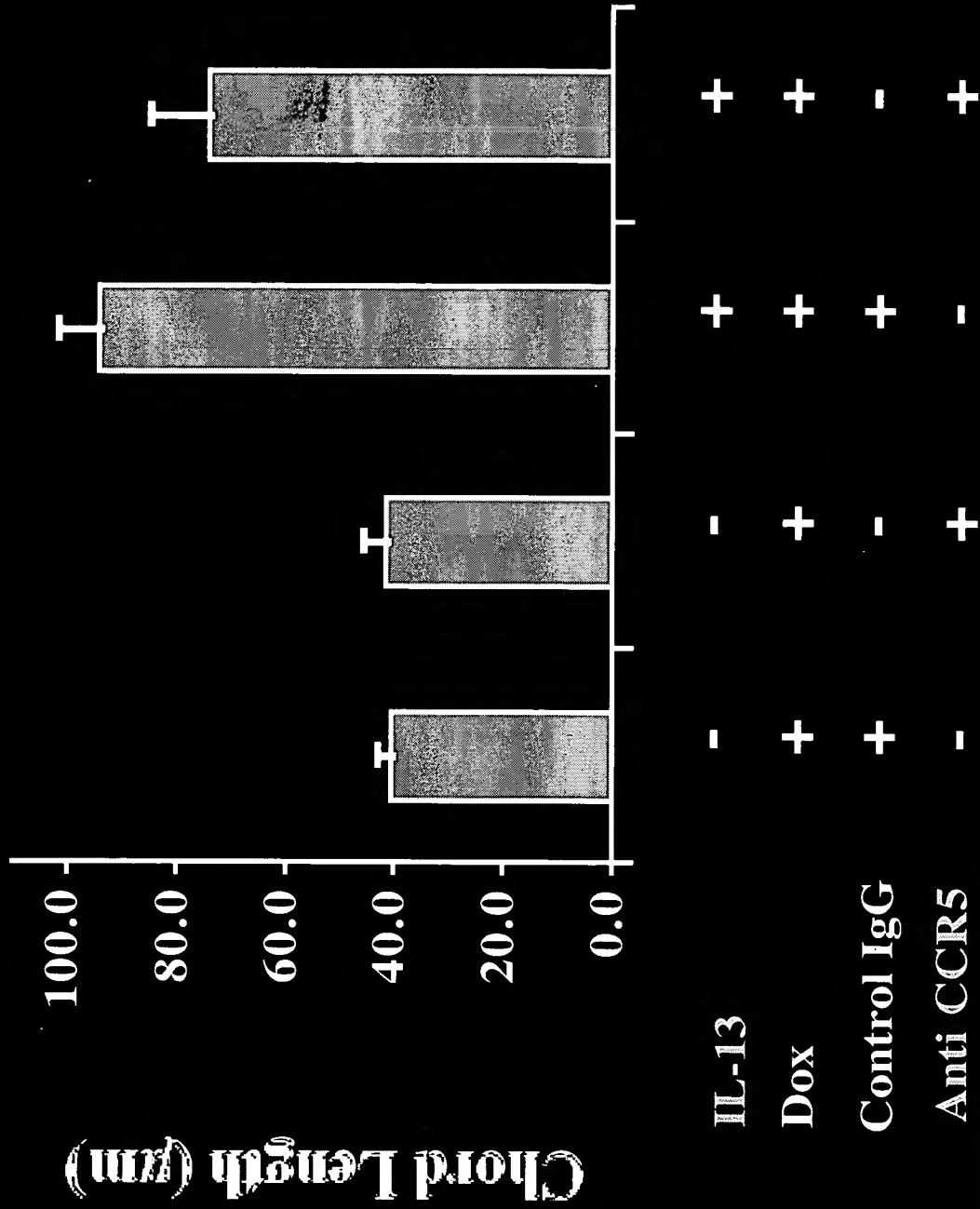
# Effect of anti-CCR5 on IL-13-induced Inflammation



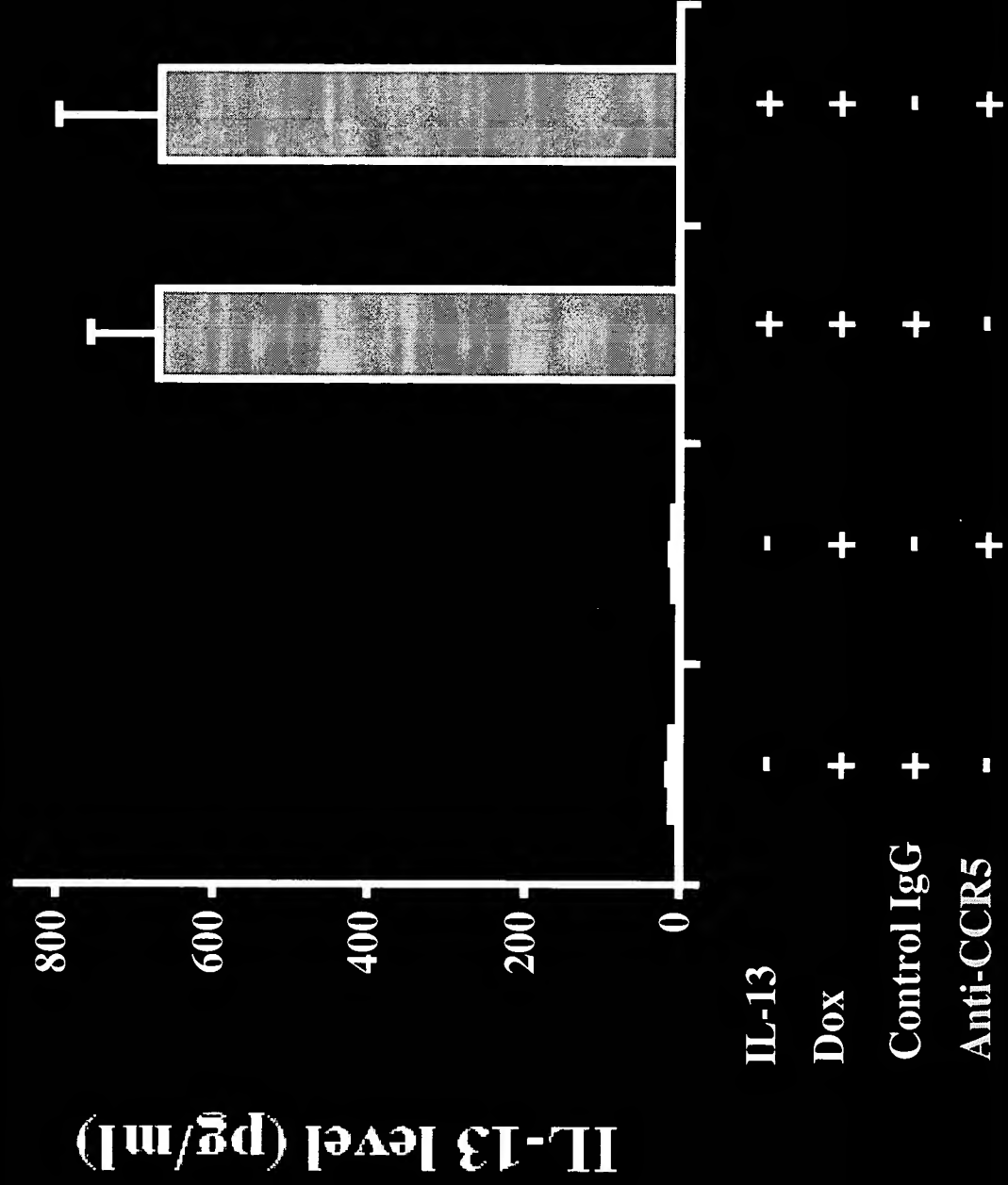
# Effect of anti-CCR5 on IL-13 induced emphysema



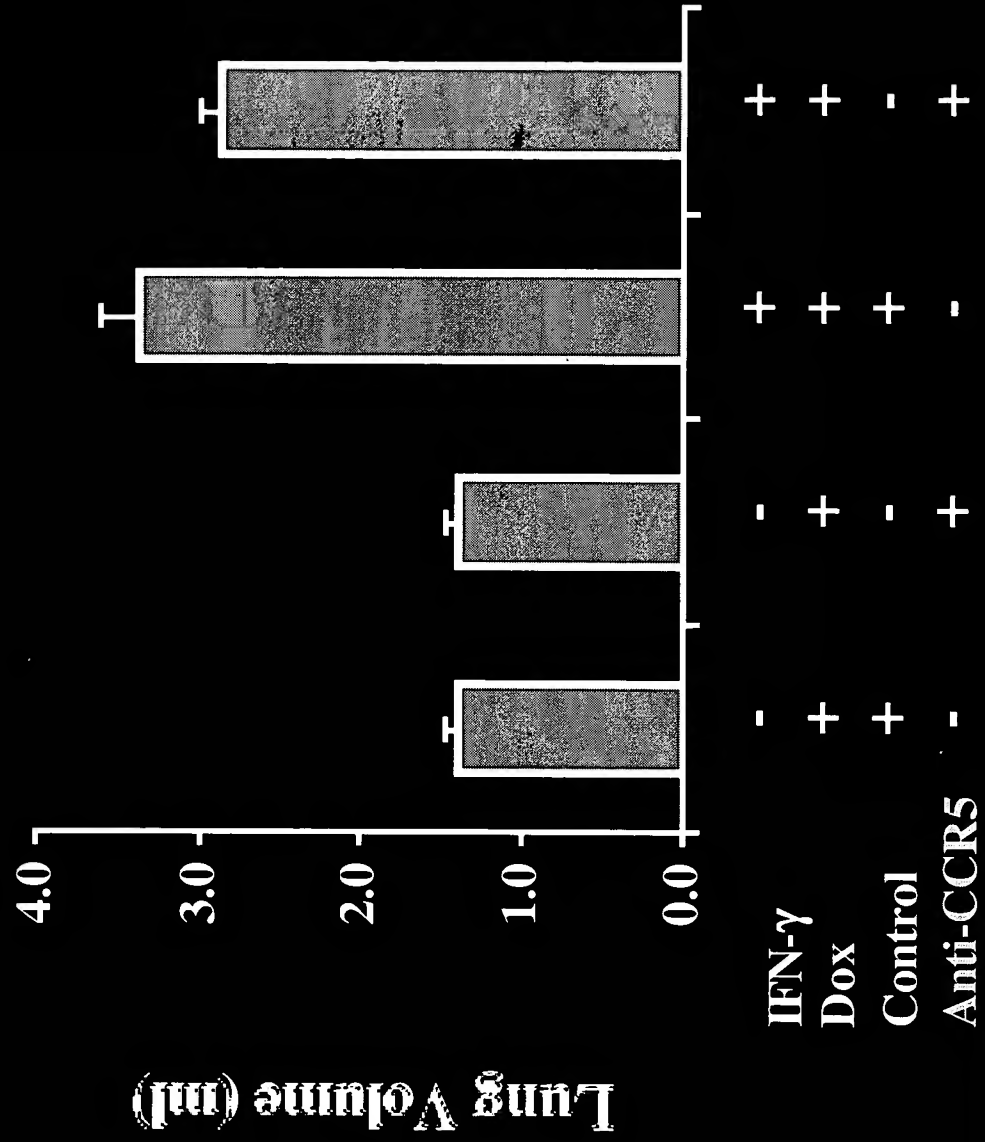
# Chord Length of Ind IL-13 mice: Effect of anti-CCR5



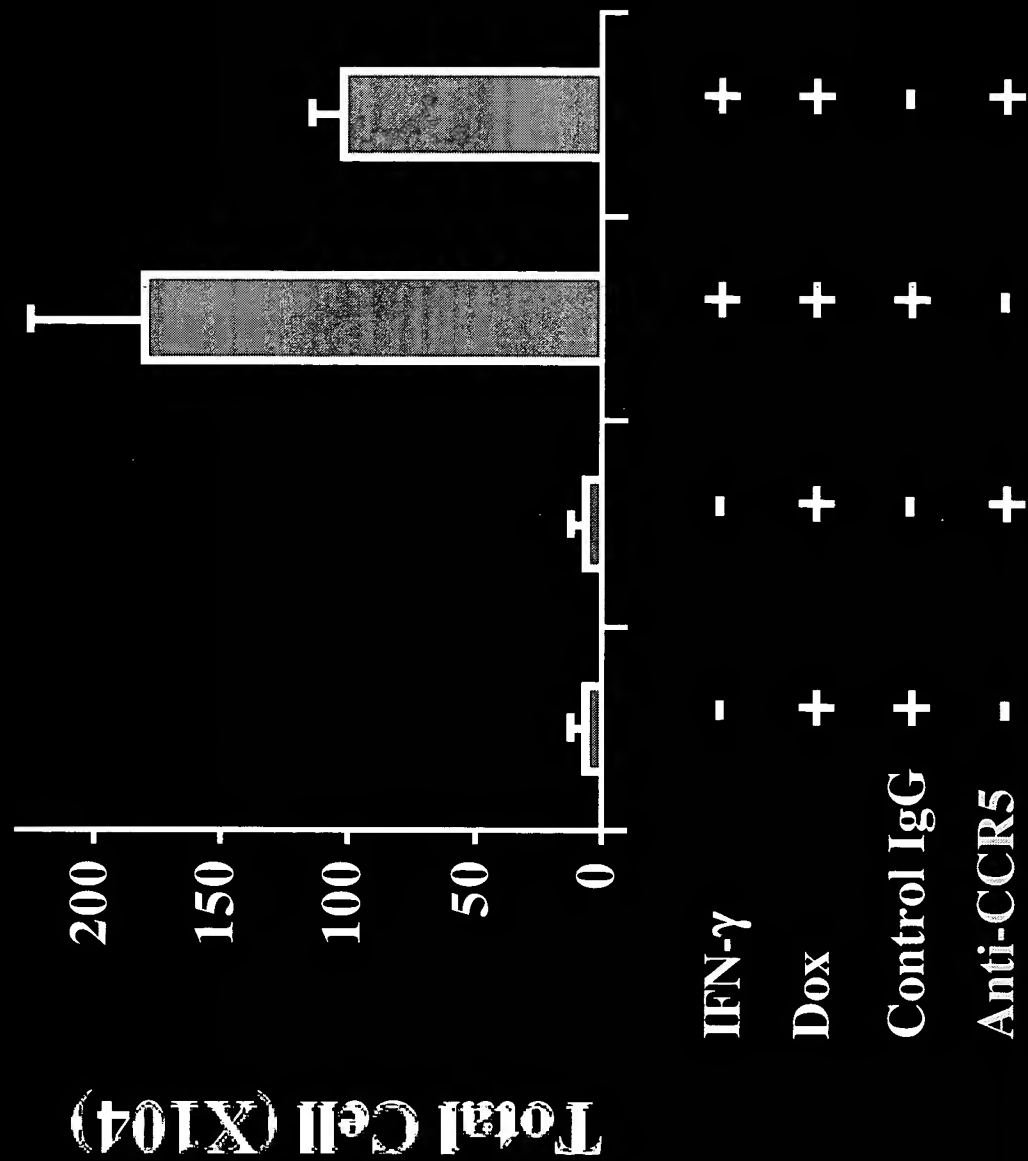
# Effect of anti-CCR5 on the levels of BAL IL-13



# Lung volume change of INF- $\gamma$ mice after anti-CCR5 treatment



# BAL total cell count of IFN- $\gamma$ mice after anti-CCR5 treatment



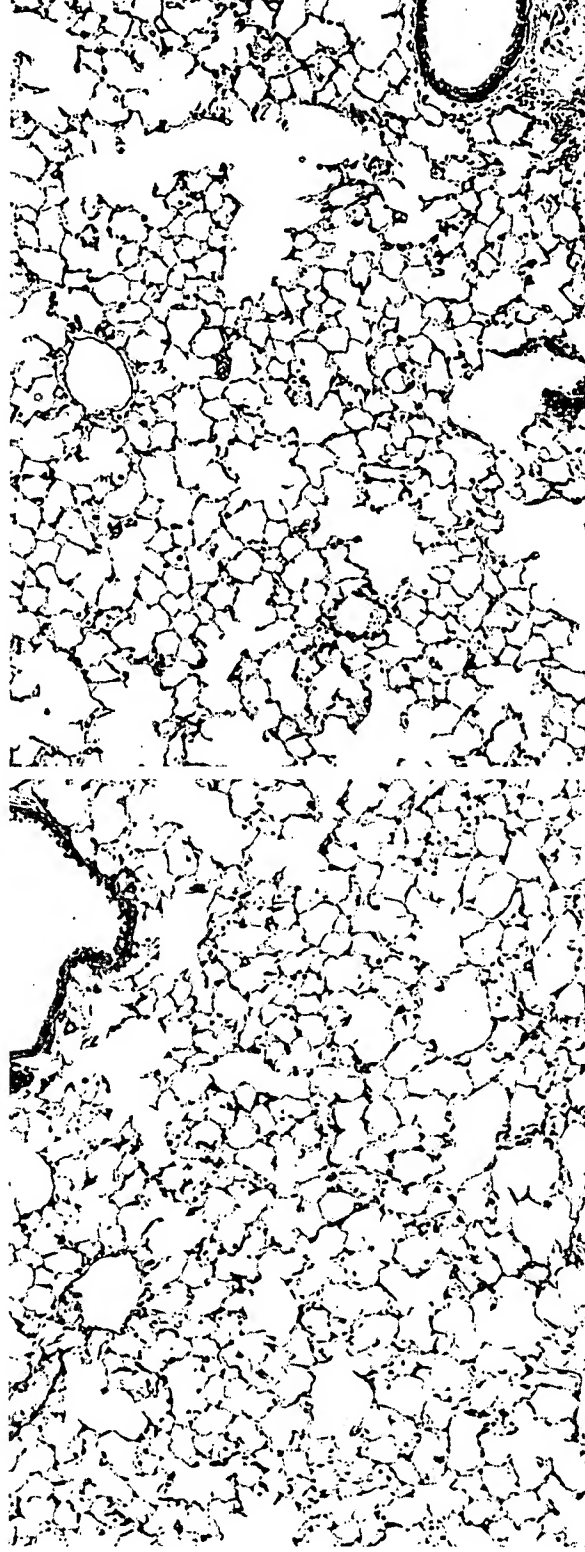
# Effect of anti-CCR5 on emphysema in CC10-IFN- $\gamma$ Lungs

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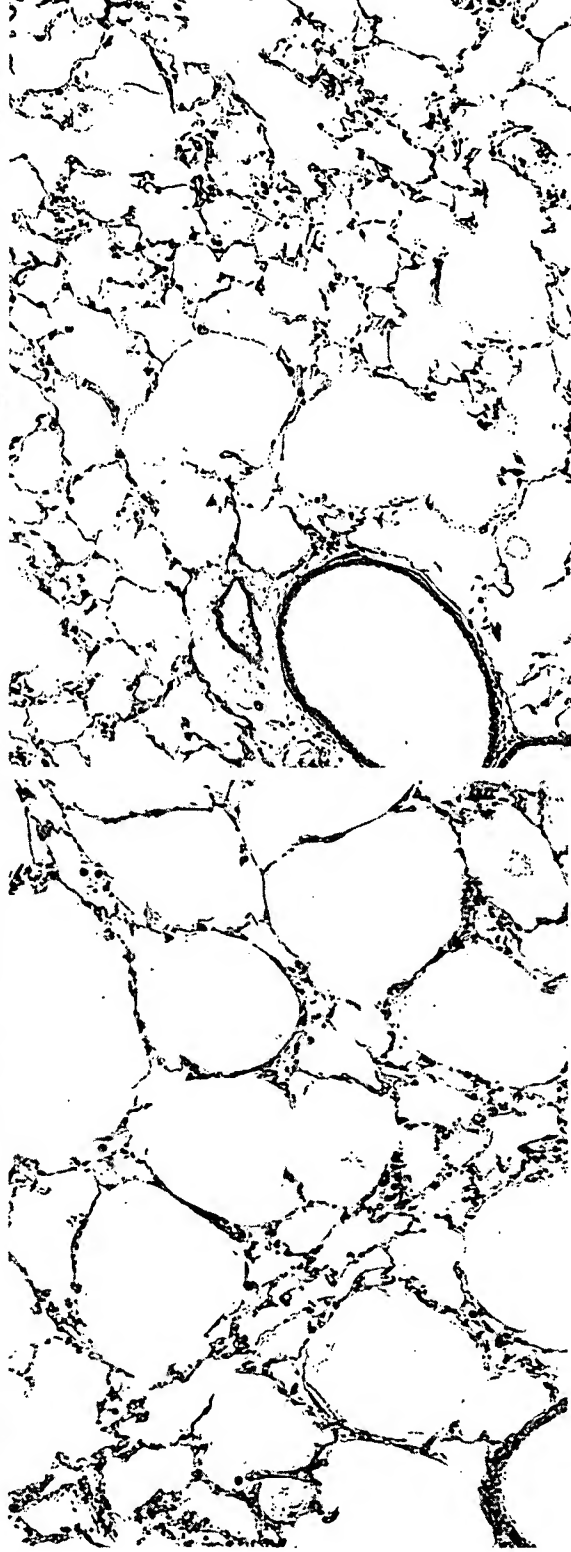
Ab control

Anti-CCR5

IFN- $\gamma$   
(-)

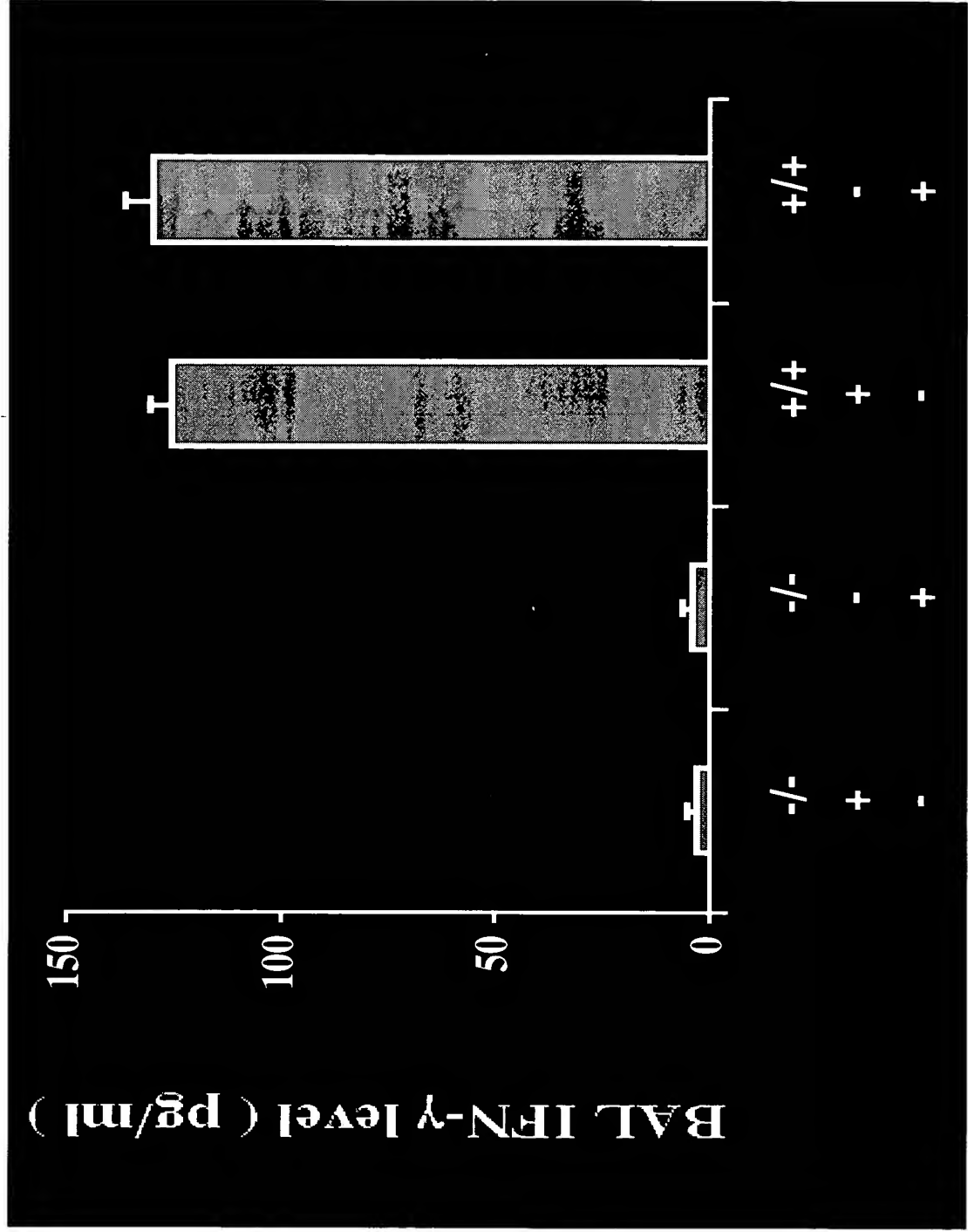


IFN- $\gamma$   
(+)

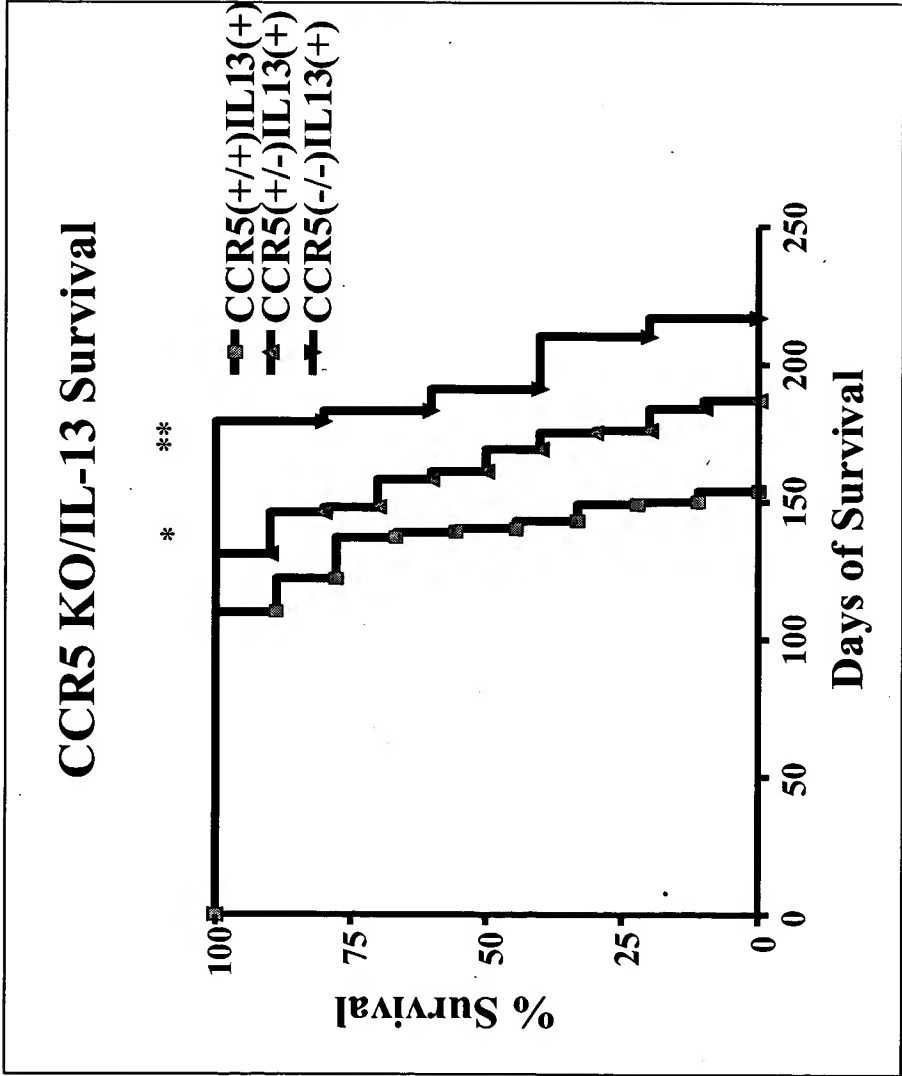




# Effect of anti-CCR 5 on BAL IFN- $\gamma$ Levels

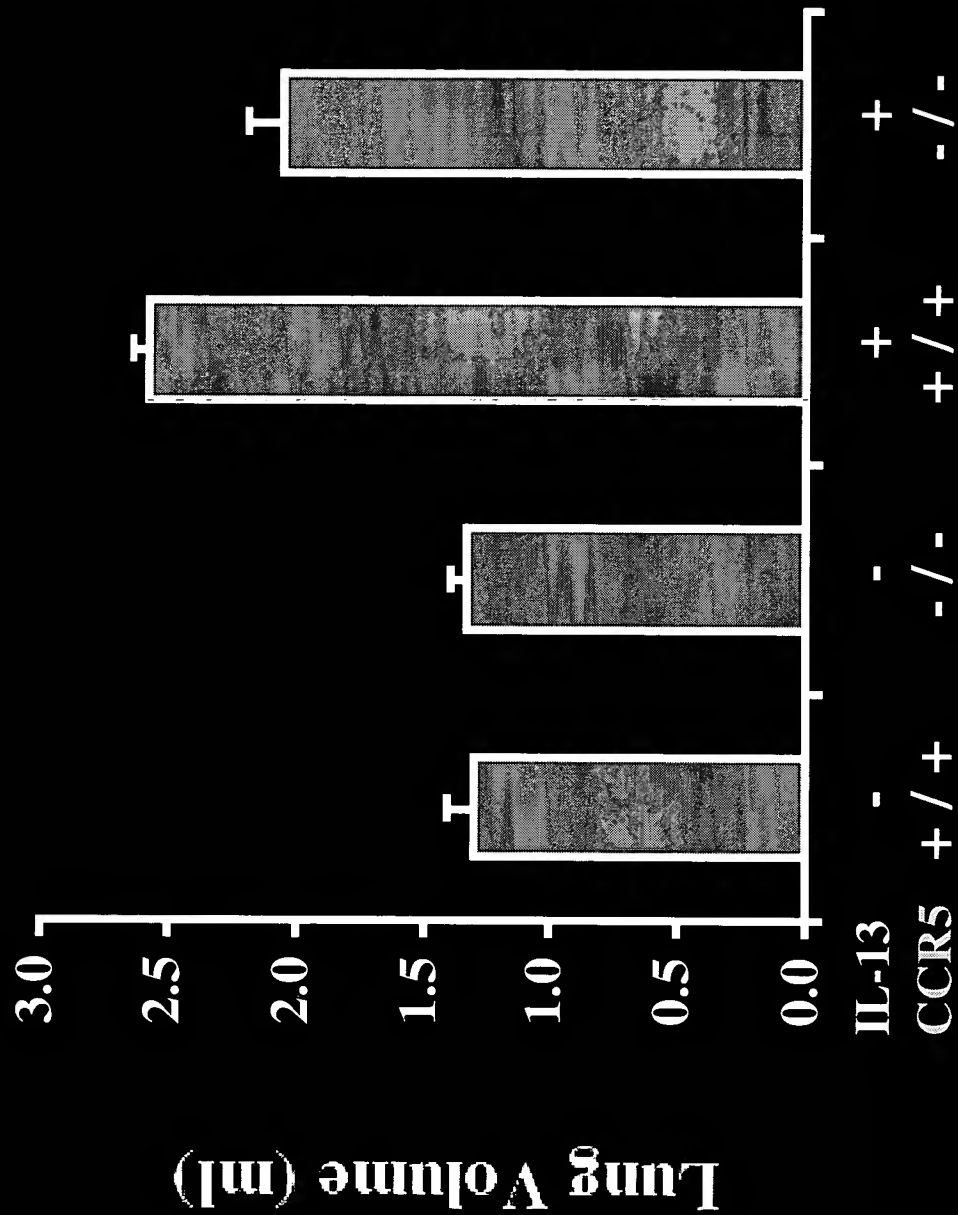


# Survival Days of CC1--IL-13 Mice with WT and Null Mutant CCR5 Loci

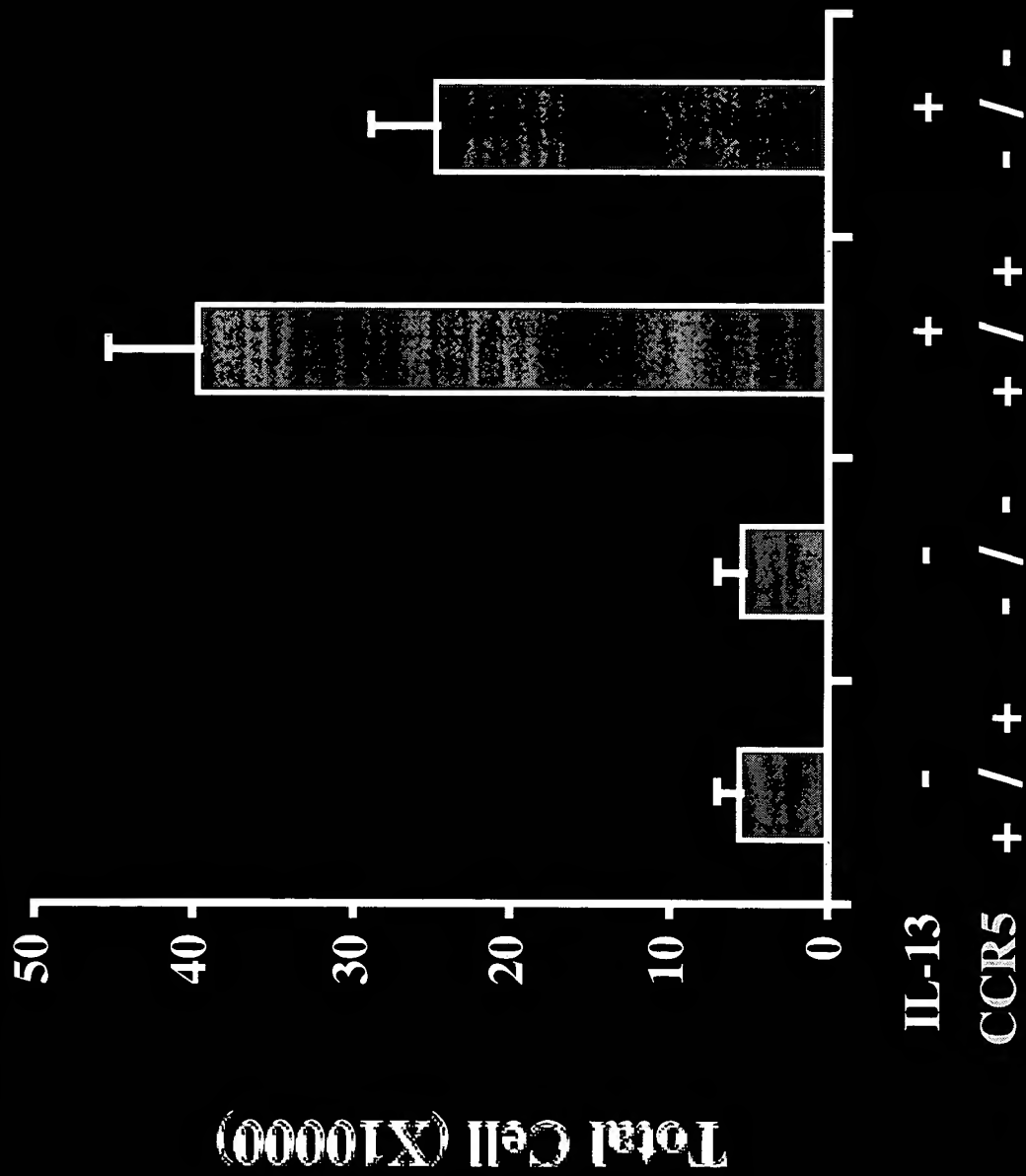


CCR5/13	n=	mean survival	P value
(+/+)(+)	9	140	
(+/-)(+)	10	165	0.0003
(-/-)(+)	5	191	0.0002

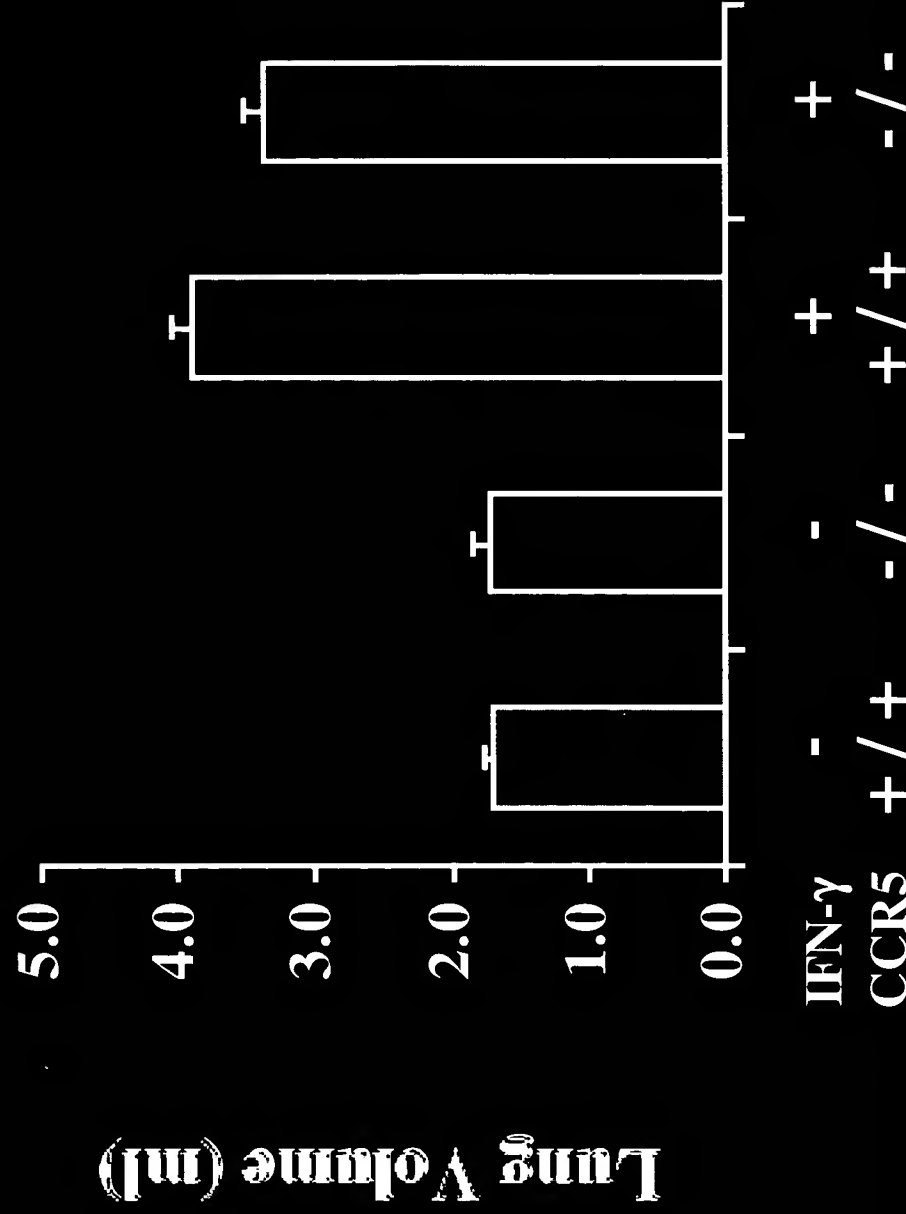
Role of CCR5 in IL-13-induced increase in lung size



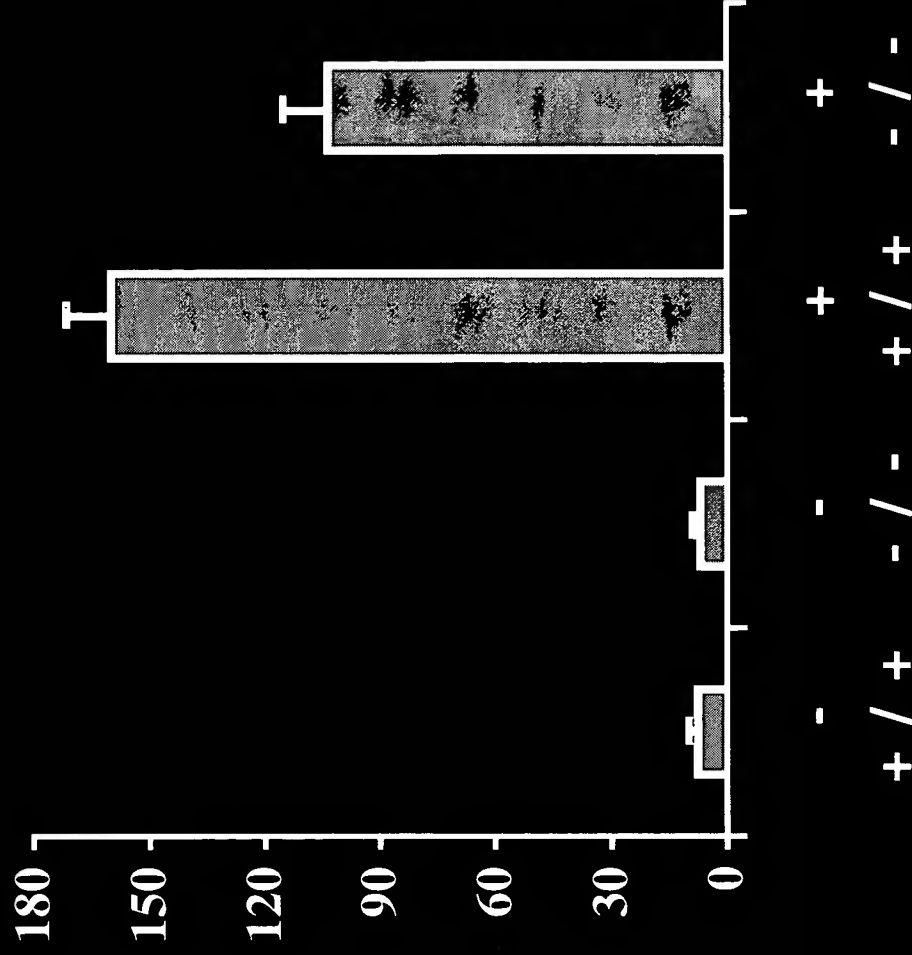
# Role of CCR5 in IL-13-induced BAL Inflammation



# Role of CCR5 in IFN- $\gamma$ -induced increase in lung size



# Role of CCR5 in IFN- $\gamma$ -induced inflammation



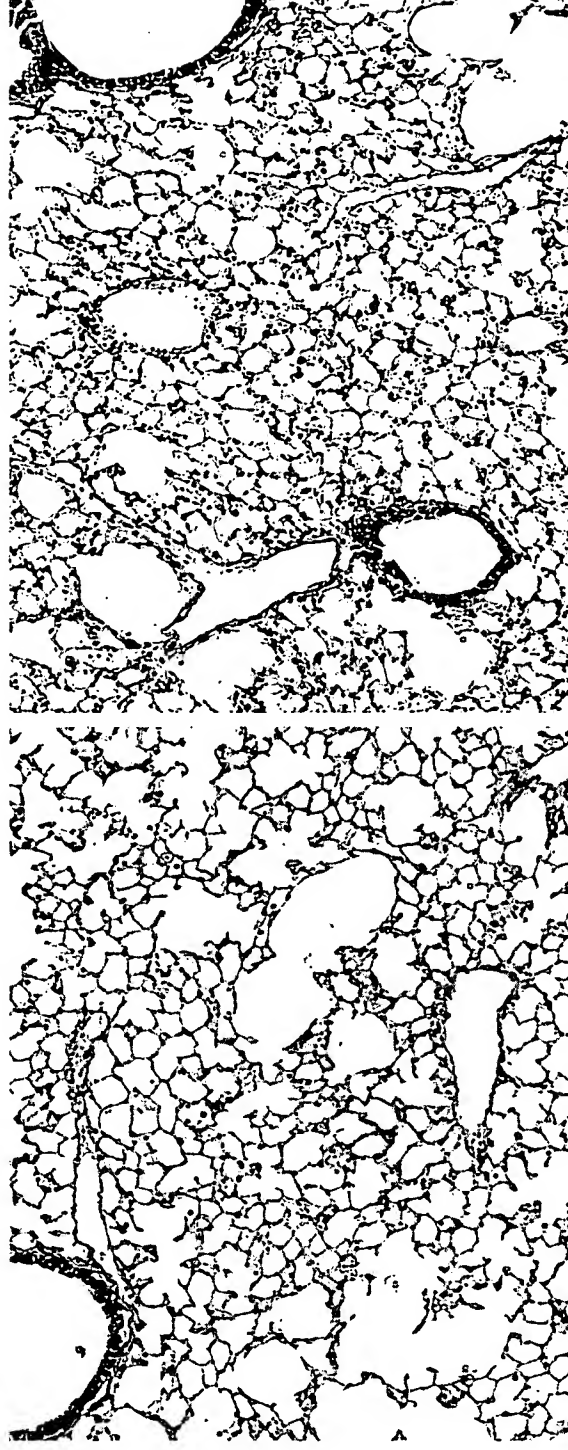
# Role of CCR5 in IFN- $\gamma$ -induced emphysema

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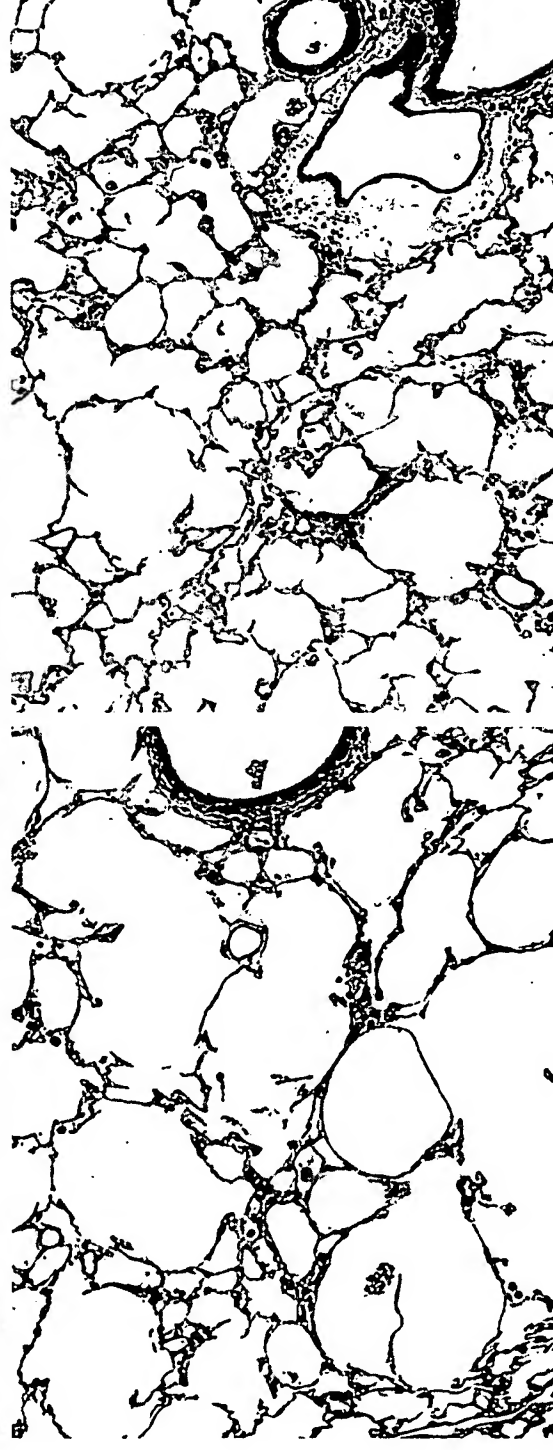
CCR5 WT

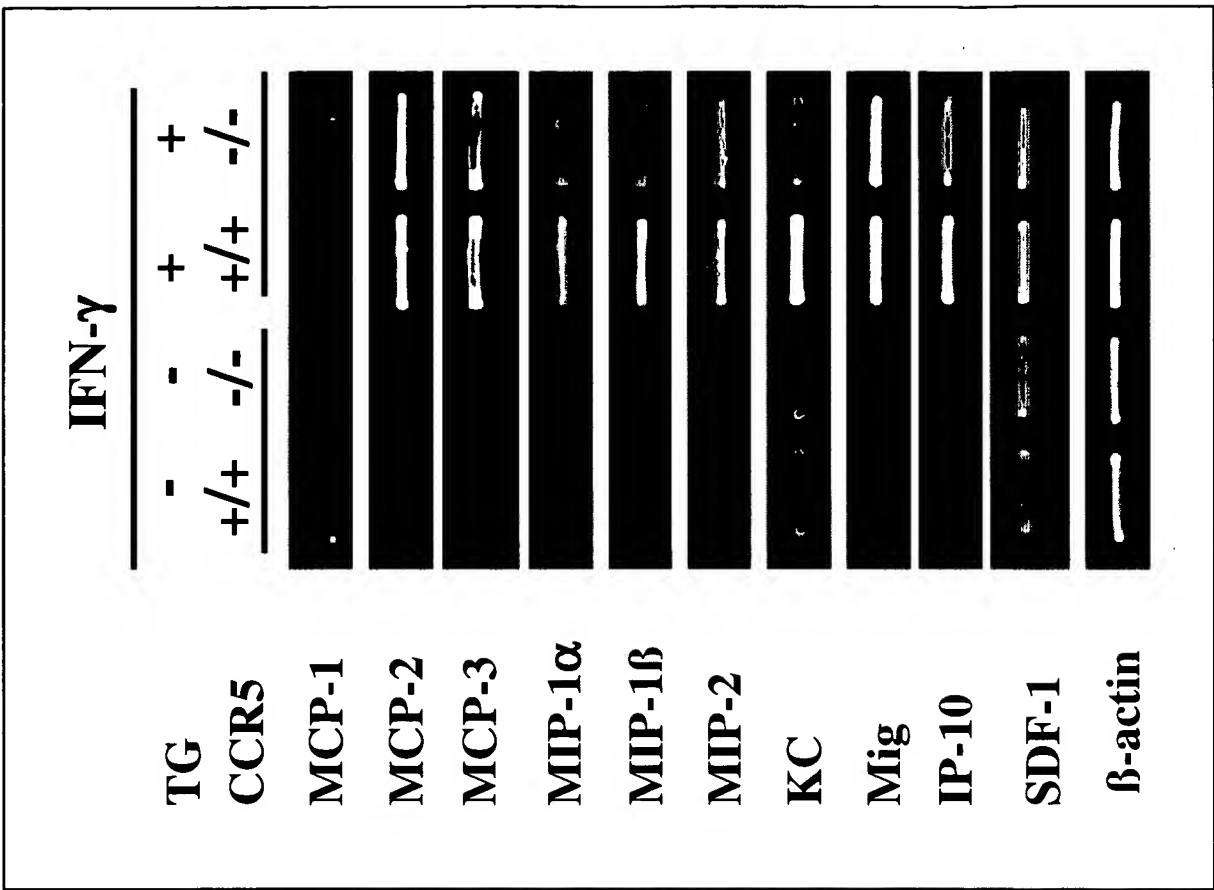
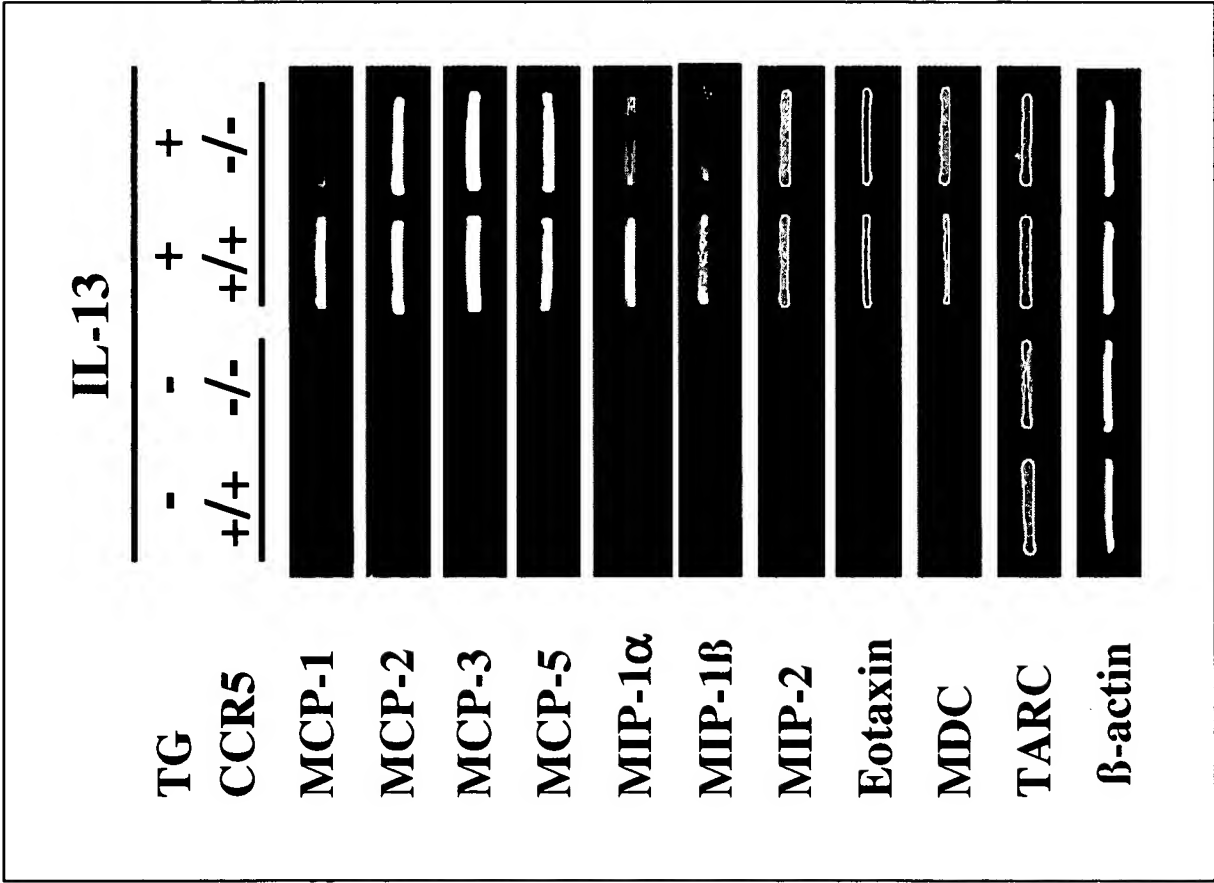
CCR5 KO

IFN- $\gamma$   
(-)



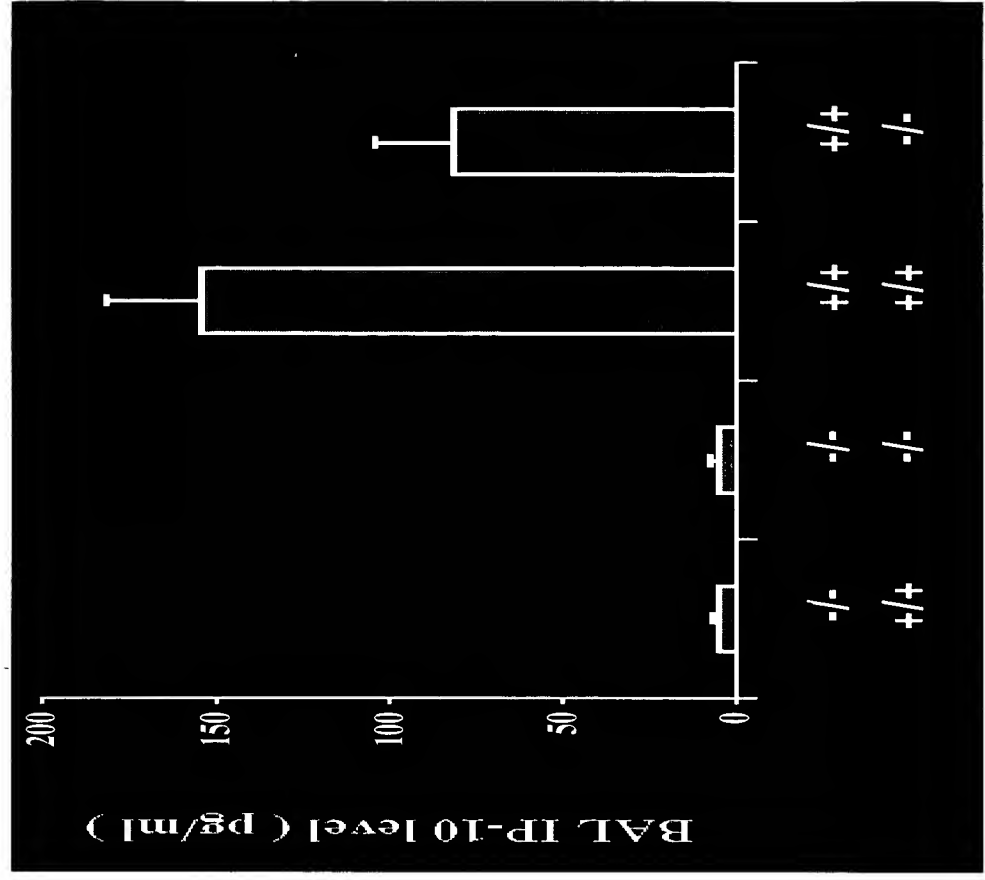
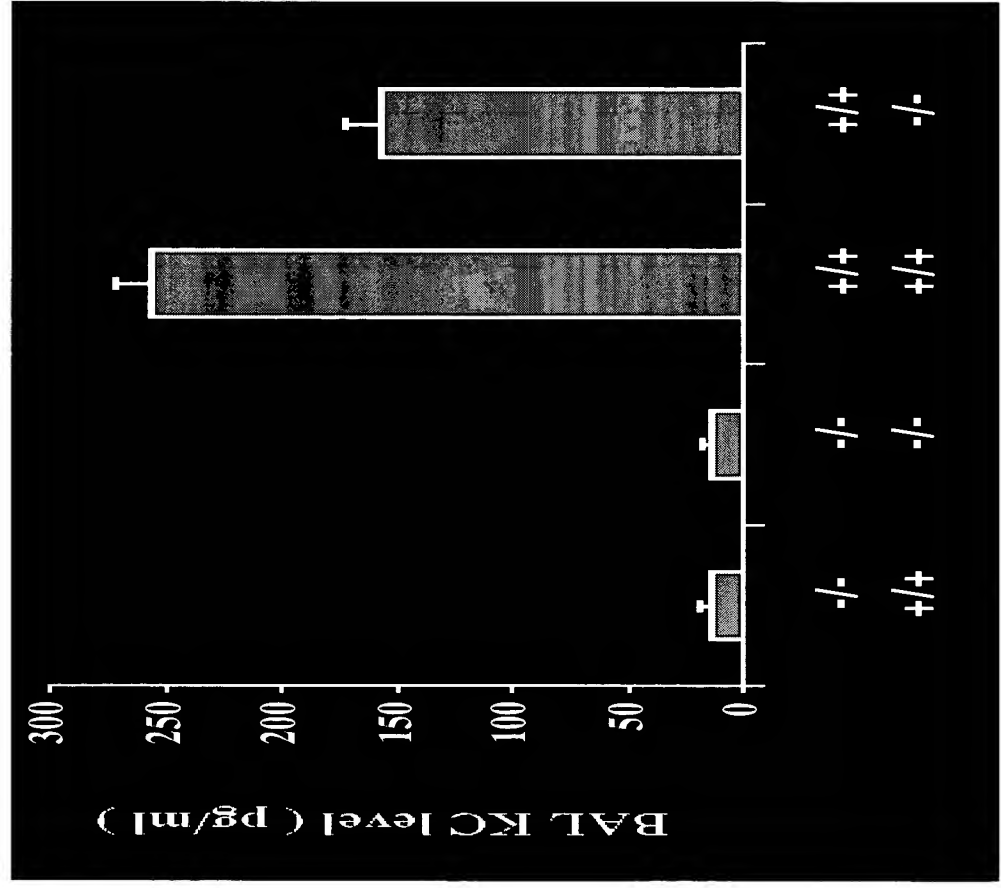
IFN- $\gamma$   
(+)



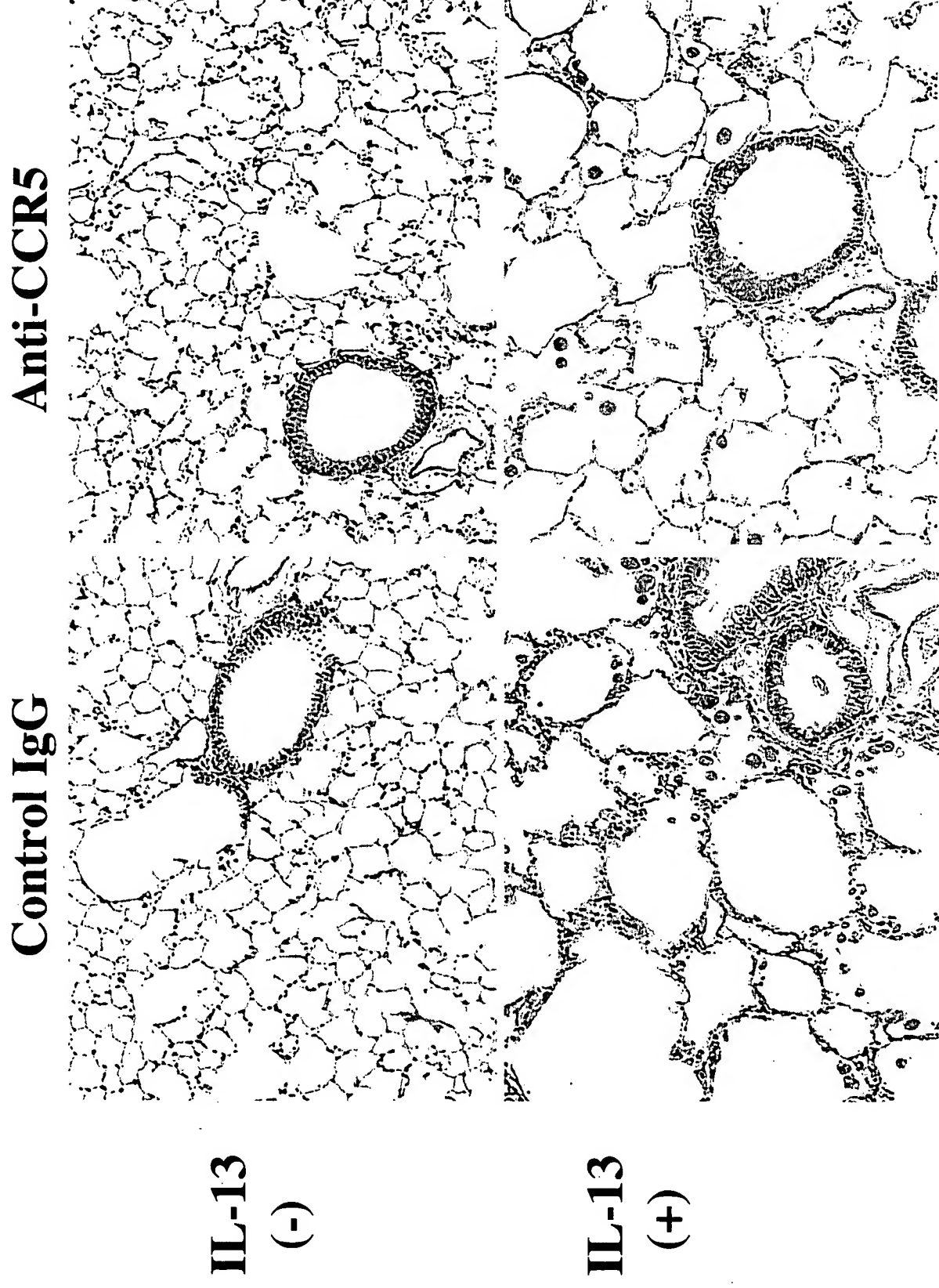




## Role of CCR5 in IFN- $\gamma$ stimulation of KC and IP-10

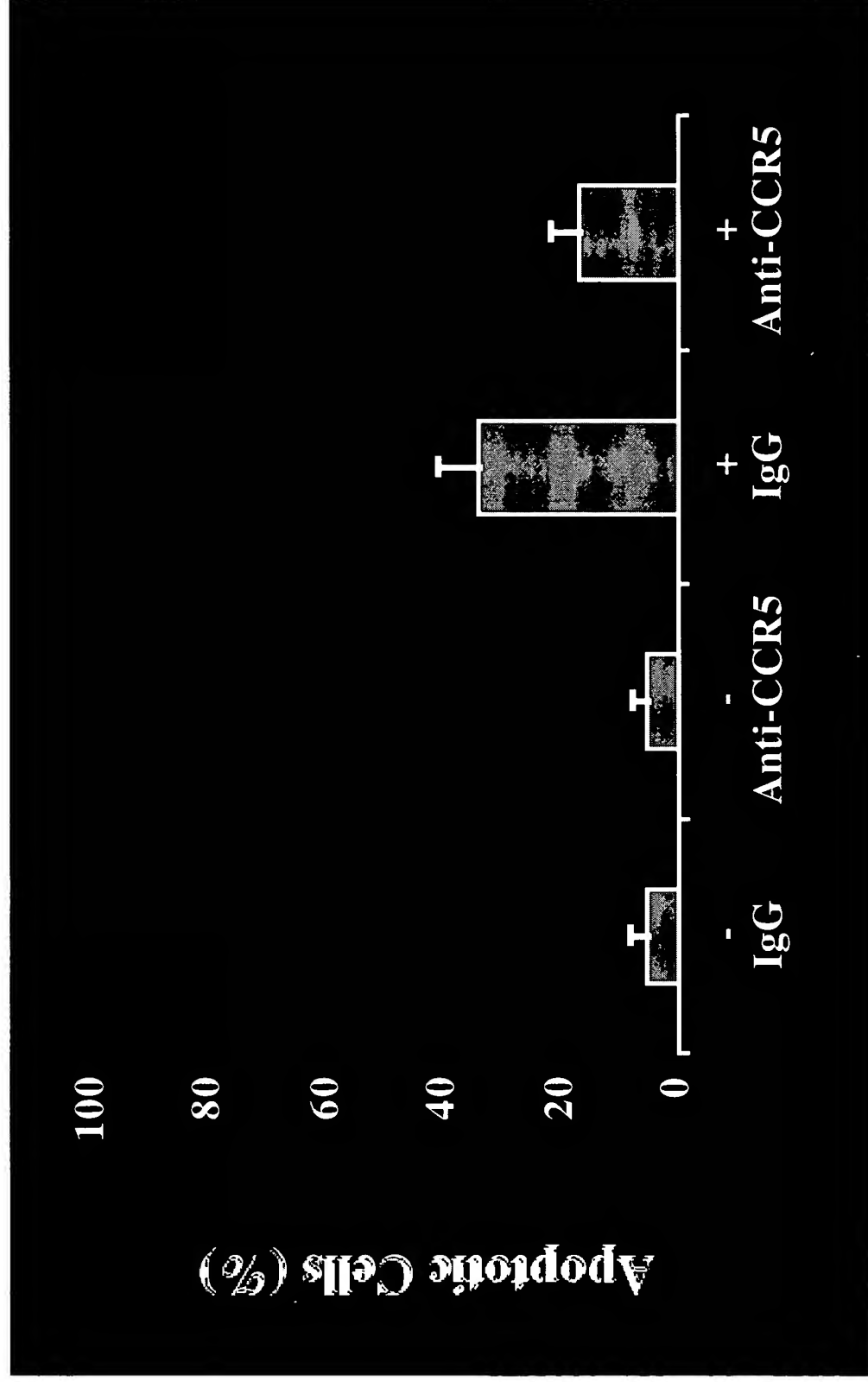


# Effect of anti-CCR5 on IL-13 induced emphysema

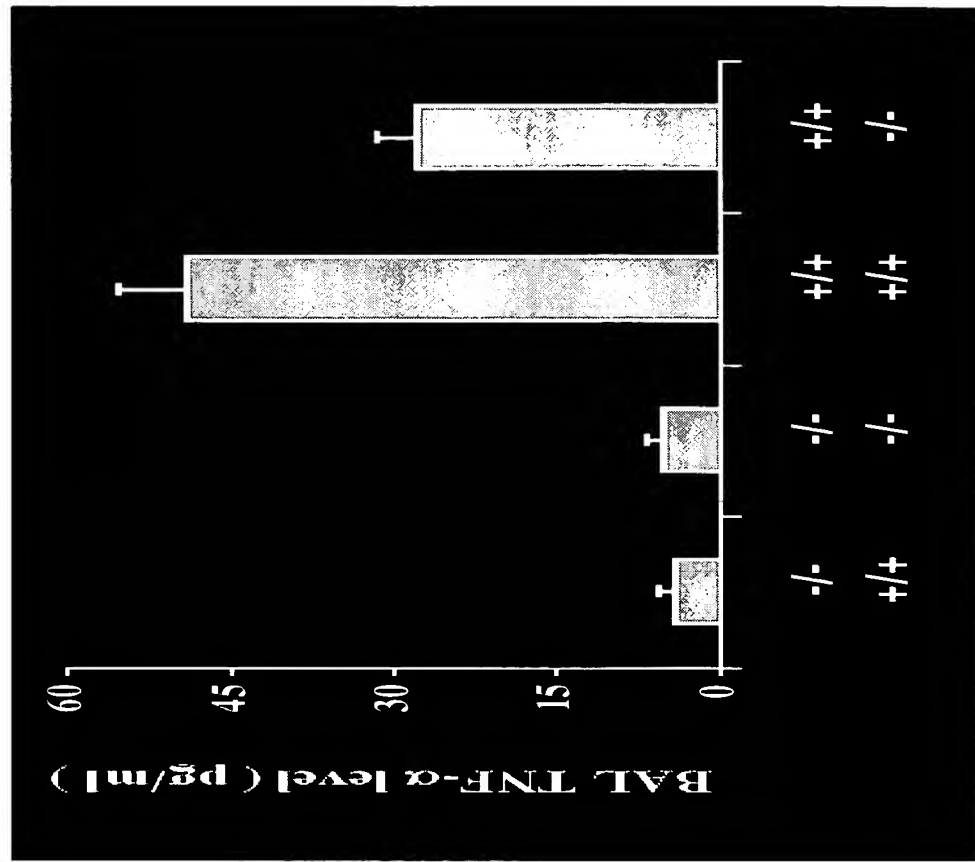
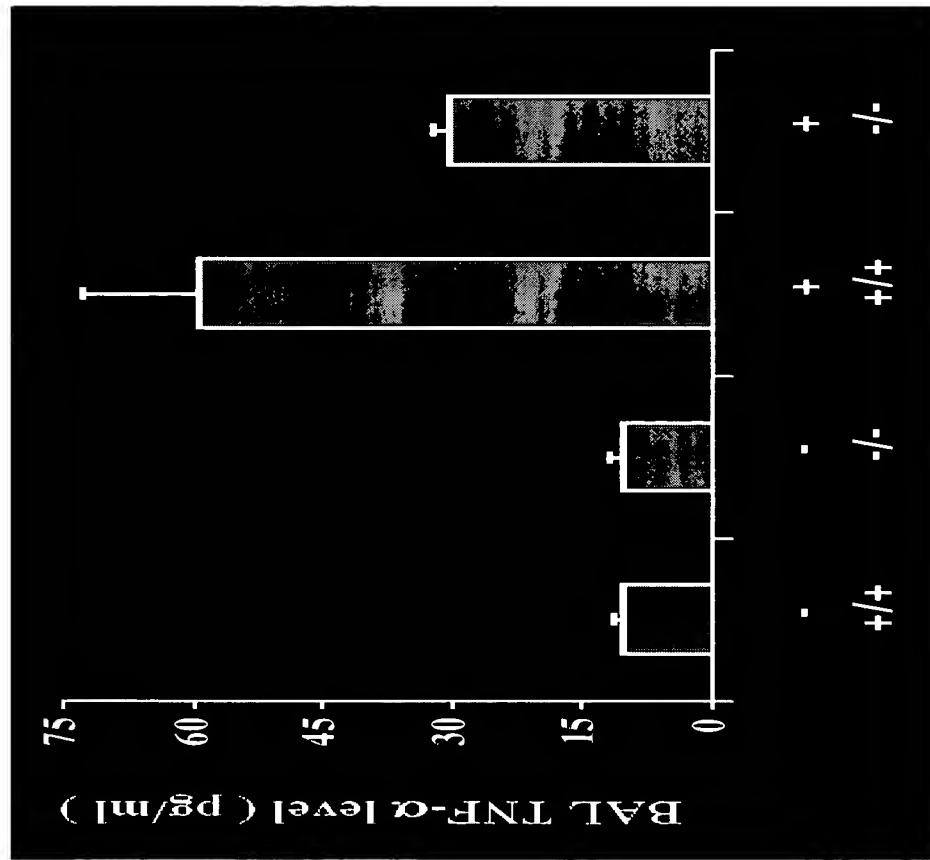


## Percentage of TUNEL (+) cells on IL-13 Mouse Lung

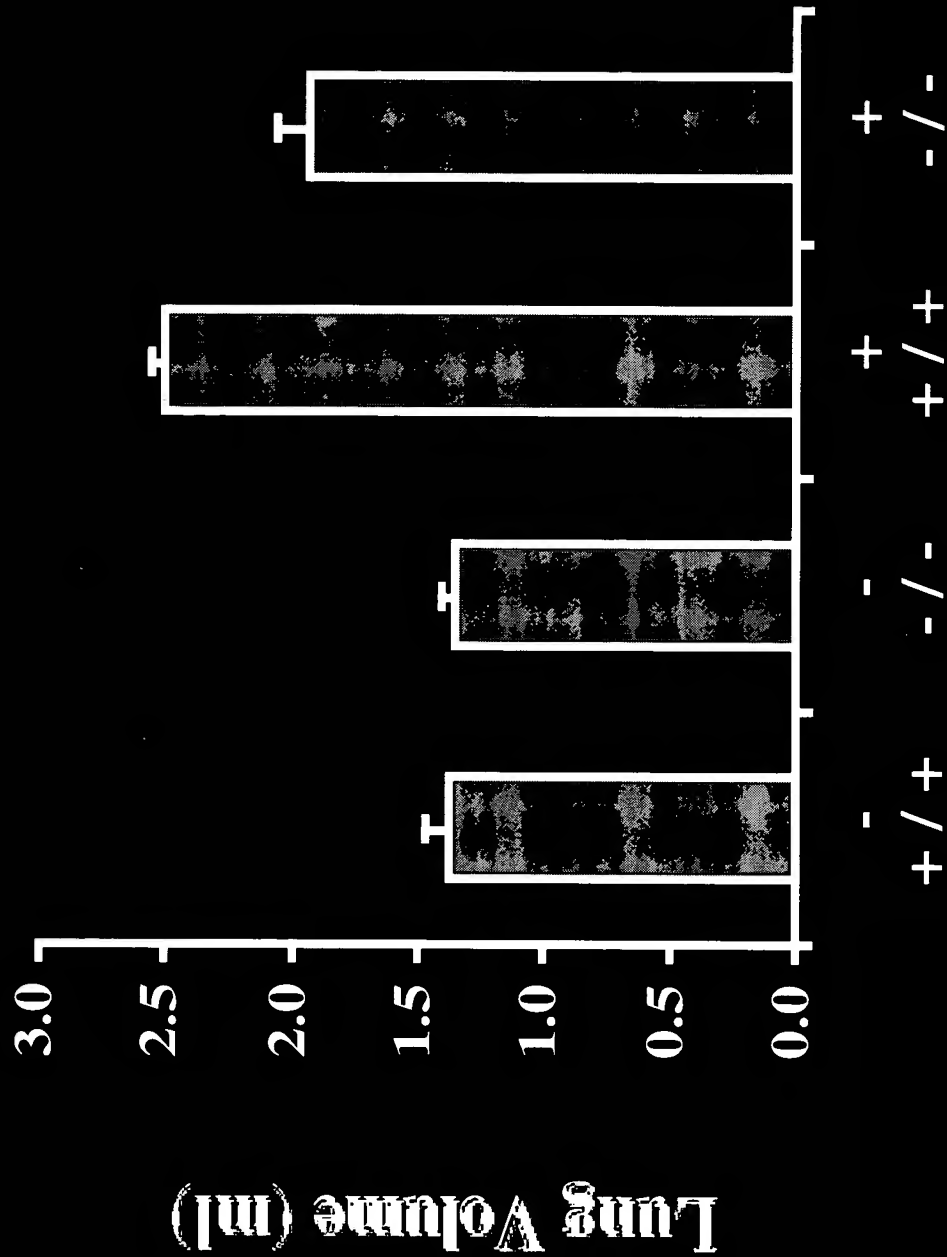
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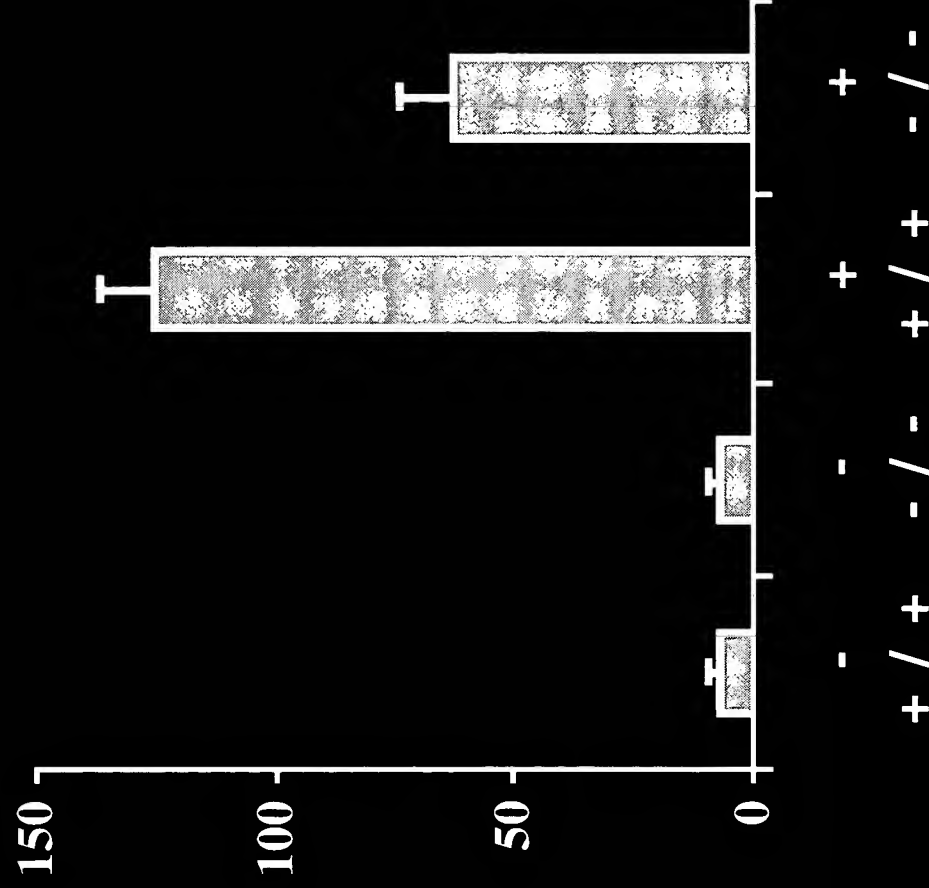
# Role of CCR5 in IL-13/ IFN- $\gamma$ induced TNF- $\alpha$ production



# Role of CCR5 in IL-4-induced increase in lung size



# Role of CCR5 in IL-4-induced BAL inflammation



# TUNEL Staining in iIL-13 Mouse Lung

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Treatment; Control IgG

Anti-CCR5

IL-13  
(-)



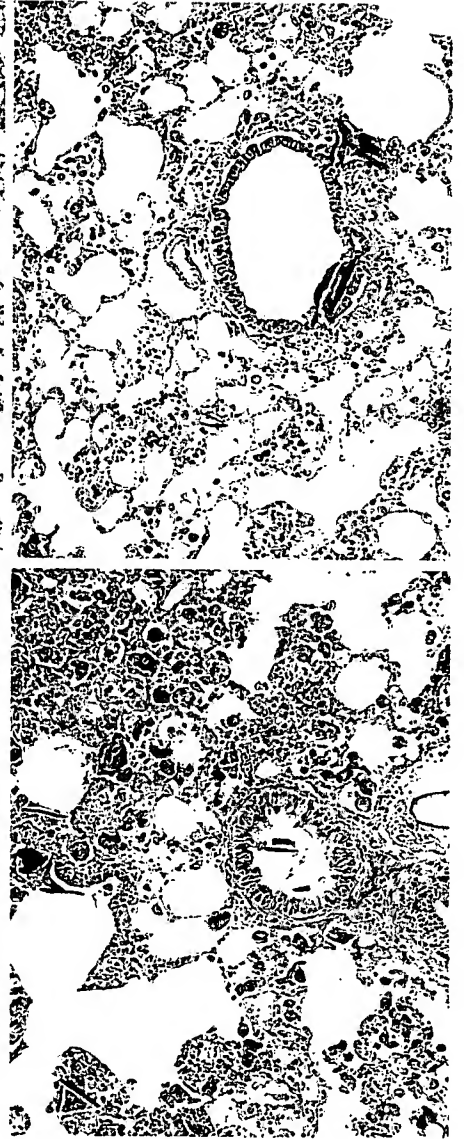
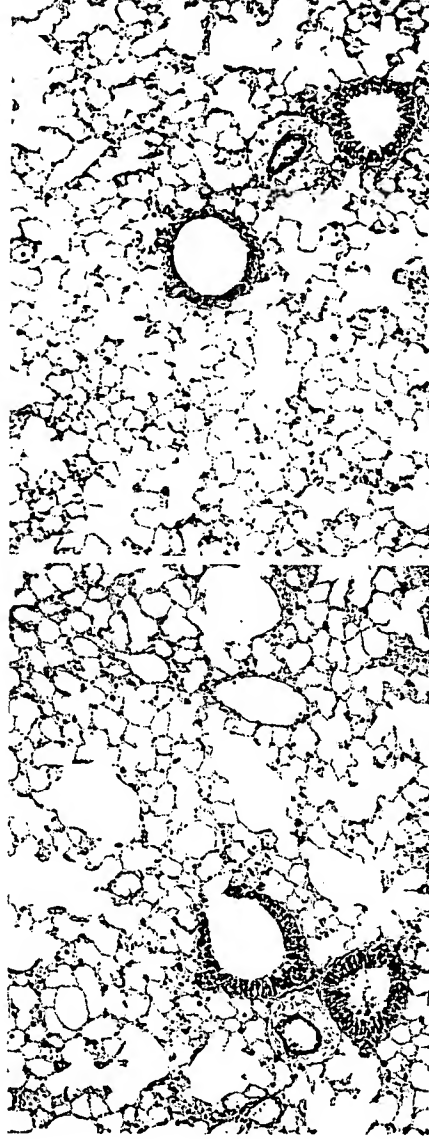
IL-13  
(+)



# Role of CCR5 in CC10-IL-4 Lung

CCR5 (+/+)

CCR5 KO



IL-4  
(-)

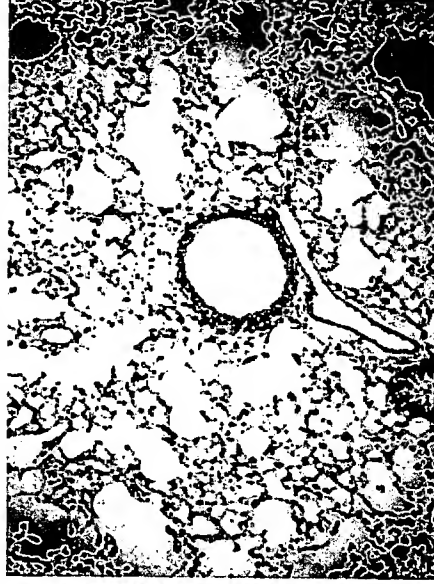
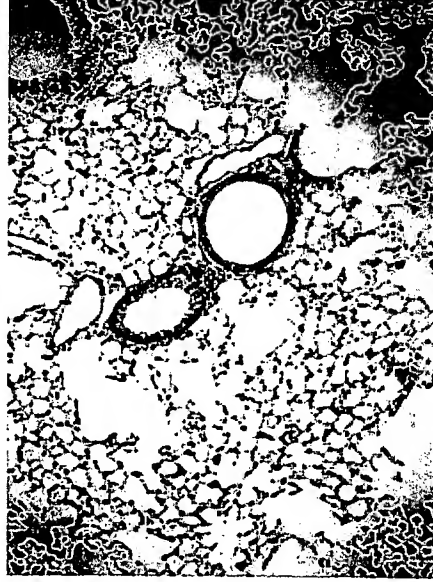
IL-4  
(+)



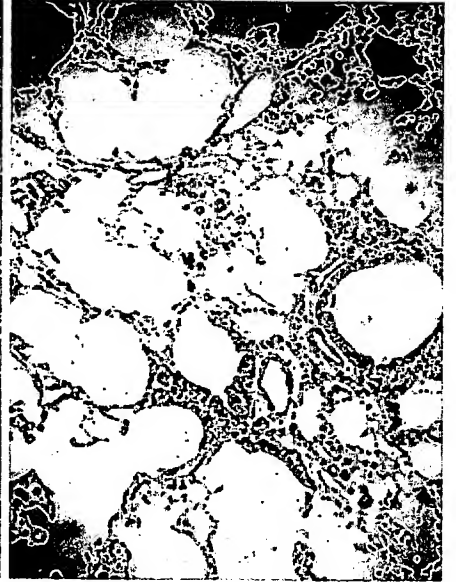
# Role of CCR5 in IL-13-induced lung phenotype

CCR5 (+/+)

CCR5 KO



IL-13  
(-)



IL-13  
(+)